

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/IB2004/002305

International filing date (day/month/year)
15.07.2004

Priority date (day/month/year)
15.07.2003

International Patent Classification (IPC) or both national classification and IPC
C07D305/12

Applicant
RANBAXY LABORATORIES LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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10/564663

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2004/002305

IAP20 Rec'd TOWPTO 13 JAN 2006

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2004/002305

Box No. II Priority

1. ☒ The following document has not been furnished:
- ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).
 - ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).
- Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. ☐ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.
4. Additional observations, if necessary:

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:
- ☒ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☐ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2004/002305

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-24
	No: Claims	25-34
Inventive step (IS)	Yes: Claims	
	No: Claims	1-34
Industrial applicability (IA)	Yes: Claims	1-34
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

PCT/IB2004/002305

Re Item IV.

The separate inventions are:

- 1) Claims 1 -24
- 2) Claims 25-33
- 3) Claim 34

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The problem associated with Claims 1-24 relates to the problem of providing a further process for preparing known compounds of formula I.

The problem associated with Claims 1-24 relates to the problem of providing a further process for preparing known compounds of formula V.

The problem associated with Claim 34 relates to the problem of providing further compounds. In this context it is to be noted that claims for products defined in terms of a process of manufacture is to be construed as a claim to the product itself.

The inventions 1)-3) relate to three separate problems with different solutions, whereby no special technical feature could be identified which defines a contribution over the prior art establishing a technical relationship over the prior art, which defines a contribution over the prior art establishing a technical relationship as required by Rule 13.2 PCT.

Re Item V.

- D1: US-A-5 902 886 (SCHICK HANS ET AL) 11 May 1999 (1999-05-11)
- D2: WO 02/32850 A (MULLINS JOHN JASON GENTRY) 25 April 2002 (2002-04-25)
- D3: ISHIHARA, TAKASHI; ICHIHARA, KAZUYOSHI, YAMANAKA, HIROKI:
"Highly Selective Aldol Reaction of Metal Enolates of alpha-Fluoropropanethioates with Aldehydes Affording erythro-alpha-Fluoro-alpha-methyl-beta-hydroxy Alkanethionates" TETRAHEDRON LETTERS, vol. 36, no. 45, 1995, pages 8267-8270, XP002300391
- D4: US-A-5 412 110 (WAGNER MARION ET AL) 2 May 1995 (1995-05-02)
- D5: US-A-4 931 463 (BARBIER PIERRE ET AL) 5 June 1990 (1990-06-05)

The problem underlying the invention is therefore to be seen in the provision of a process having improved effects compared with the D1 process, wherein such effects must be shown to have their origins in the distinguishing feature/s of the invention. In the absence of any evidence for such effects an inventive step cannot be acknowledged.

It is therefore considered that the present claims 1- 24 lack inventive step.

Invention 2

Novelty

Claims 25 to 33 are not novel in view of the disclosures of D6 - see passages cited in the International Search Report.

Inventive Step

The closest prior art is considered to be D6, in view of the novelty destroying subject matter that this contains.

The subject matter of claims 25-33 is obvious in the light of the disclosures of D6.

Invention 3

a product is not rendered novel merely by the fact that it is produced by means of a new process. As indicated in the section on unity products defined in terms of a process of manufacture is to be construed as a claim to the product itself.

It follows from claim 1, that the compounds prepared by the process described in claim 34 are compounds of formula I.

Thus, the compound (3S,4S)-3-hexyl-4-[(3S)-2-hydroxy-tridecyl]-2-oxetanone disclosed in D6 (see compound of formula III' and column 13, lines 24 and 25) anticipates compounds of formula I and are thus novelty destroying to the present claim 34.

In view of the fact that the isomerism at the double bonds undecadienyl group nor the specific enantiomers of the compound of formula III, D8 is not novelty destroying to the present claim 34.

D6: US-A-4 983 746 (BARBIER PIERRE ET AL) 8 January 1991 (1991-01-08)
D7: EP-A-1 127 886 (HOFFMANN LA ROCHE) 29 August 2001 (2001-08-29)
D8: US-A-4 202 824 (AOYAGI, TAKAAKI ET AL) 13 May 1980 (1980-05-13)

Invention 1

Novelty

The process of the present claims 1-24 differ from that disclosed in D1 through the TBDMS protecting group.

The process of the present claims 1-24 differs from that disclosed in D2 inter alia through the use of the metal enolate.

The process of the present claims 1-24 differs from that disclosed in D1 (see reaction scheme on page 8268 and first full paragraph) through the structure of oxetanone formed (cf the C_6H_{13} group and the $R^1CH(OH)CH_2$ - group).

Inventive Step

The closest prior art is considered to be D1, since this discloses a similar process for preparing diastomerically pure oxetan-2-ones, which are identical to those falling under claim 1 of the application

Thus Example 3 of D1 describes the preparation and separation (3S,4S)-3-hexyl-4-[(2S)-2-hydroxytridecyl]oxetan-2-one and (3R,4R)-3-hexyl-4-[(2S)-2-hydroxytridecyl]oxetan-2-one, the former corresponding to the compound of formula I.

The only difference between the claimed process and that of D1 is that TBDMS is used as a protecting group, rather than the 2-methoxyprop-2-yl group.

The skilled person wishing to provide a further process for preparing the desired end product would try alternative protective groups to the 2-methoxyprop-2-yl group used in the D1 procedure with the expectation that these would also be suitable.

Inventive Step

In view of the disclosure of (3S,4S)-3-hexyl-4-[(3S)-2-hydroxy-tridecyl]-2-oxetanone in D8 the subject matter of claim 34 is obvious.

Re Item VII

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description, nor are these documents identified therein.

Re Item VIII

a double bond appears to be missing in formula III in claim 1,

In example 4 in the description (page 14) the formula in the title is incomplete.

The abbreviation TBDMS has not been defined in the claims.